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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/554,157	09/13/2006	**Benjamin Oshlack**	Y2428-00047	7637

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EXAMINER	
SHEIKH, HUMERA N	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/554,157	OSHLACK ET AL.	
	Examiner	Art Unit	
	Humera N. Sheikh	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *1-16 and 32-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-31 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/20/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Receipt is acknowledged of the Response to Restriction Requirement filed 07/23/10 and the Information Disclosure Statement (IDS) filed 10/20/05.

Applicant's election with traverse of Group III (claims 17-31) in the reply filed on 23 July 2010 is acknowledged. The traversal is on the ground(s) that "Each of the five groups comprises co-extruded particles, which also comprise an adverse agent and a sheath. Further, the Examiner cites to the same subclass of class 424 as classification of four of the five groups of inventions." This is not found persuasive because as stated in the Restriction Requirement, each of the groups are distinct in that they provide unique dosage forms in terms of for example, their administration forms (i.e., oral versus non-oral) and entail unique process steps and procedures with respect to the method of making and method of treating pain in a patient. The particular features and elements of one group are not necessarily required for the other group. Thus, the different groups would have distinct issues with respect to patentability, enablement, written description, etc. Art anticipating Group I would not necessarily anticipate nor render obvious the invention of Groups II-V. Hence, the products and/or methods of making/treating are mutually exclusive and distinct, each from the other.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-16 and 32-46 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 23 July 2010.

Claims 1-47 are pending in this action.

Claims 1-16 and 32-46 have been withdrawn (based on non-elected invention).

Claims 17-31 and 47 have been examined in this action.

Claims 17-31 and 47 are rejected.

* * * * *

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 20 October 2005 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

* * * * *

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17-31 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oshlack *et al.* (U.S. Pat. No. 6,696,088).

Oshlack *et al.* ('088) teach an oral dosage form comprising (i) an opioid agonist in releasable form and (ii) a sequestered opioid antagonist which is substantially not released when the dosage form is administered intact, such that the ratio of the amount of antagonist released from said dosage form after tampering to the amount of said antagonist released from said intact dosage form is about 4:1 or greater, based on the in-vitro dissolution at 1 hour of said dosage form in 900 ml of Simulated Gastric Fluid using a USP Type II (paddle) apparatus at 75 rpm at 37°C, wherein said agonist and antagonist are interdispersed and are not isolated from each other in two distinct layers (see Abstract). Oshlack also teaches a method of treating pain in human patients with an oral dosage form of an opioid agonist while reducing its misuse by oral, parenteral, intranasal and/or sublingual route (col. 3, line 66 – col. 4, line 3).

An objective of the invention is to provide an oral dosage form containing an effective dose of opioid agonist along with a dose of opioid antagonist which does not change the analgesic efficacy of the opioid agonist when the dosage form is orally administered intact, but

which can prevent abuse if the dosage form is tampered with by interfering with the effect of the opioid agonist (col. 3, lines 45-51).

In one embodiment, the invention is directed to an oral dosage form comprising an opioid agonist and naltrexone or a salt thereof in a substantially non-releasable form; wherein the agonist and naltrexone are at least partially interdispersed (see col. 6, lines 14-19).

Oshlack teach that when the antagonist is in the form of multiparticulates coated with a sequestering material, the multiparticulates can be in the form of inert beads coated with the antagonist and overcoated with the material or alternatively in the form of a granulation comprising the antagonist and the material. The multiparticulates can be dispersed in a matrix comprising the opioid agonist or contained in a capsule with the opioid agonist (col. 6, lines 24-32). See also column 5, lines 54-65. Oshlack teaches opioid antagonist particles in a coating that substantially prevents release of the antagonist; the coating comprising an acceptable hydrophobic material. Suitable hydrophobic materials disclosed include cellulose polymers and acrylic polymers that are insoluble in the gastrointestinal fluids and impermeable to the opioid antagonist (col. 9, lines 31-51); (col. 14, lines 15-20); (col. 19, line 20 – col. 20, line 42). These hydrophobic materials read on the hydrophobic materials of instant claims 22 and 23.

Oshlack also teach that the antagonist may be dispersed in a matrix comprising a sequestering material, which substantially prevents the release of the antagonist, and the matrix can be in the form of pellets. The pellets can be dispersed in another matrix comprising the opioid agonist or contained in a capsule with the opioid agonist. In another embodiment, part of the antagonist is in a matrix and/or part of the antagonist is in a coated bead (col. 6, lines 33-41). See also column 5, lines 54-65. The dosage form of the invention can also be provided in the

form of compressed tablets, whereby the opioid antagonist is coated with a coating and then mixed with the opioid agonist (col. 9, line 58 – col. 10, line 2). These teachings read on the tablet and capsule of instant claims 28 and 29. See also column 21, lines 35-43.

Oshack teaches that, in certain embodiments of the invention, the substantially non-releasable form of the opioid antagonist is vulnerable to mechanical, thermal and/or chemical tampering, e.g., tampering by means of crushing, shearing, grinding, chewing and/or dissolution in a solvent in combination with heating of the oral dosage form. When thus tampered with, the integrity of the substantially non-releasable form of the opioid antagonist will be compromised, and the opioid antagonist will be made available to be released (col. 8, line 64 – col. 9, line 14). Oshlack teaches that the opioid antagonist which is sequestered, e.g., is not bioavailable when the dosage is administered intact but is bioavailable when the dosage form is tampered with (e.g., in an attempt to misuse the dose of the opioid analgesic) (col. 3, lines 52-58).

Oshlack teaches that the release of the opioid agonist from the oral dosage form is at such a rate that blood (e.g., plasma) concentrations (levels) are maintained within the therapeutic range (above the minimum effective analgesic concentration) but below toxic levels over a period of 8 to 24 hours, preferably over a time period indicative of a twice-a-day or once-a-day formulation (col. 11, lines 10-17).

Preferably, the opioid agonist may be selected from the group consisting of morphine, hydromorphone, hydrocodone, oxycodone, codeine, levorphanol, meperidine, methadone and mixtures thereof (col. 10, lines 3-6); (col. 14, lines 20-54). In certain preferred embodiments of the invention, the opioid agonist comprises hydrocodone, oxycodone or pharmaceutically acceptable salts thereof (col. 10, lines 35-37). These agonists read on those of instant claims 24

and 25. The opioid agonist is provided in sustained release form, which reads on the "controlled release" of opioid agonist instantly claimed (col. 11, lines 10-17); (col. 21, line 44 - col. 22, line 7).

Preferred examples of the opioid antagonist include naltrexone, naloxone, nalmefene, cyclazacine, levallorphan, pharmaceutically acceptable salts thereof and mixtures thereof (col. 10, lines 7-10); (col. 16, lines 21-25). In certain preferred embodiments of the invention, the opioid antagonist, present in a substantially non-releasable form, comprises naloxone, naltrexone, or pharmaceutically acceptable salts thereof (col. 10, lines 37-40). These antagonists read on those of instant claims 26 and 27.

The sustained-release particles of the opioid agonist have a diameter of about 0.1 mm to about 2.5 mm (col. 22, lines 36-40). The particles of the opioid antagonist are about 0.2 to about 2 mm in diameter (col. 9, lines 52-57). These particle sizes read on the "about 0.1 mm to about 3.0 mm" of instant claim 20.

The process for preparing sustained-release matrices are obtained via melt-granulation or melt-extrusion techniques to yield extruded multi-particulates provided within a capsule or extruded multi-particulates provided within a compressed tablet (col. 30, line 8 - col. 32, line 42). This reads on the "co-extruded" second particles of instant claim 17.

Oshlack teaches the release of the second particles being "less than 0.25 mg", which reads on and falls within the "about 0.5 mg or less" and "about 0.05 mg or less" of instant claims 30 and 31. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed.Cir. 1990). Moreover, it is

the Examiner's position that it is deemed obvious to one of ordinary skill in the art to determine suitable or effective levels of release through the use of routine or manipulative experimentation to obtain the best possible results, as these are variable parameters attainable within the art.

Summarily, the prior art clearly teaches and recognizes oral opioid agonist/antagonist combination formulations, whereby the opioid agonist is provided in controlled release form and the opioid antagonist is in sequestered form, in which the antagonist is substantially not released when the dosage form is administered intact. Oshlack *et al.* also teach that the oral dosage form contains an effective dose of opioid agonist along with a dose of opioid antagonist which does not change the analgesic efficacy of the opioid agonist when the dosage form is orally administered intact, but which can prevent abuse if the dosage form is tampered with by interfering with the effect of the opioid agonist. Thus, given the teachings of Oshlack *et al.*, the instant invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

* * * * *

Claims 17-31 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Breder *et al.* (U.S. Pat. Appln. Pub. No. 2003/0157168 A1).

Breder *et al.* ('168) teach an oral dosage form comprising (i) an opioid agonist in releasable form and (ii) a sequestered opioid antagonist which is substantially not released when the dosage form is administered intact, such that the ratio of the mean C_{max} of the antagonist after single dose oral administration of the dosage form after tampering to the mean C_{max} of the antagonist after single dose oral administration of an intact dosage form is at least 1.5:1 (see

Abstract). Breder also teaches a method of treating pain in human patients and decreasing the abuse of an opioid agonist in an oral dosage form (page 4, ¶ 0050-0053).

Breder teach that when the antagonist is in the form of multiparticulates coated with a sequestering material, the multiparticulates can be in the form of inert beads coated with the antagonist and overcoated with the material or alternatively in the form of a granulation comprising the antagonist and the material. The multiparticulates can be dispersed in a matrix comprising the opioid agonist or contained in a capsule with the opioid agonist (p. 4, ¶ 0047-0049). Breder teaches opioid antagonist particles in a coating that substantially prevents release of the antagonist; the coating comprising an acceptable hydrophobic material. Suitable hydrophobic materials disclosed include cellulose polymers and acrylic polymers that are insoluble in the gastrointestinal fluids and impermeable to the opioid antagonist (p. 10, ¶ 0123-0131). These hydrophobic materials read on the hydrophobic materials of instant claims 22 and 23.

Breder also teach that the antagonist may be dispersed in a matrix comprising a sequestering material, which substantially prevents the release of the antagonist, and the matrix can be in the form of pellets. The pellets can be dispersed in another matrix comprising the opioid agonist or contained in a capsule with the opioid agonist. In another embodiment, part of the antagonist is in a matrix and/or part of the antagonist is in a coated bead (p. 4, ¶ 0047). The dosage form of the invention can also be provided in the form of compressed tablets, whereby the opioid antagonist is coated with a coating and then mixed with the opioid agonist (p. 6, ¶ 0071). These teachings read on the tablet and capsule of instant claims 28 and 29. See also (p. 12, ¶ 0137.

Breder teaches that, in certain embodiments of the invention, the substantially non-releasable form of the opioid antagonist is vulnerable to mechanical, thermal and/or chemical tampering, e.g., tampering by means of crushing, shearing, grinding, chewing and/or dissolution in a solvent in combination with heating of the oral dosage form. When thus tampered with, the integrity of the substantially non-releasable form of the opioid antagonist will be compromised, and the opioid antagonist will be made available to be released (p. 5, ¶ 0061). Breder teaches that the opioid antagonist which is sequestered, e.g., is not bioavailable when the dosage is administered intact but is bioavailable when the dosage form is tampered with (e.g., in an attempt to misuse the dose of the opioid analgesic) (p. 5, ¶ 0057).

Breder teaches that the release of the opioid agonist from the oral dosage form is at such a rate that blood (e.g., plasma) concentrations (levels) are maintained within the therapeutic range (above the minimum effective analgesic concentration) but below toxic levels over a period of 8 to 24 hours, preferably over a time period indicative of a twice-a-day or once-a-day formulation (p. 6, ¶ 0073).

Preferably, the opioid agonist may be selected from the group consisting of morphine, hydromorphone, hydrocodone, oxycodone, codeine, levorphanol, meperidine, methadone and mixtures thereof (p. 5, ¶ 0068). In certain preferred embodiments of the invention, the opioid agonist comprises hydrocodone, oxycodone or pharmaceutically acceptable salts thereof (p. 6, ¶ 0070). These agonists read on those of instant claims 24 and 25. The opioid agonist is provided in sustained release form, which reads on the "controlled release" of opioid agonist instantly claimed (p. 12, ¶ 0137).

Preferred examples of the opioid antagonist include naltrexone, naloxone, nalmefene, cyclazacine, levallorphan, pharmaceutically acceptable salts thereof and mixtures thereof (p. 5, ¶ 0068). In certain preferred embodiments of the invention, the opioid antagonist, present in a substantially non-releasable form, comprises naloxone, naltrexone, or pharmaceutically acceptable salts thereof (p. 6, ¶ 0070). These antagonists read on those of instant claims 26 and 27.

The sustained-release particles of the opioid agonist have a diameter of about 0.1 mm to about 2.5 mm (p. 12, ¶ 0142). The particles of the opioid antagonist are about 0.2 to about 2 mm in diameter (p. 5, ¶ 0066). These particle sizes read on the "about 0.1 mm to about 3.0 mm" of instant claim 20.

The process for preparing sustained-release matrices are obtained via melt-granulation or melt-extrusion techniques to yield extruded multi-particulates provided within a capsule or extruded multi-particulates provided within a compressed tablet (p. 16, ¶ 0194-0213). This reads on the "co-extruded" second particles of instant claim 17.

With regards to the rate of release of the second particles (being "about 0.5 mg or less" and "about 0.05 mg or less" as in instant claims 30/31), it is the Examiner's position that it is deemed obvious to one of ordinary skill in the art to determine suitable or effective levels of release through the use of routine or manipulative experimentation to obtain the best possible results, as these are variable parameters attainable within the art.

Summarily, the prior art clearly teaches and recognizes oral opioid agonist/antagonist combination formulations, whereby the opioid agonist is provided in controlled release form and the opioid antagonist is in sequestered form, in which the antagonist is substantially not released

when the dosage form is administered intact. Breder *et al.* also teach that the oral dosage form contains an effective dose of opioid agonist along with a dose of opioid antagonist which does not change the analgesic efficacy of the opioid agonist when the dosage form is orally administered intact, but which can prevent abuse if the dosage form is tampered with by interfering with the effect of the opioid agonist. Thus, given the teachings of Breder *et al.*, the instant invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

* * * * *

Conclusion

--No claims are allowed at this time.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (571) 272-0604. The examiner can normally be reached on Monday-Friday during regular business hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax, can be reached on (571) 272-0623. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Humera N. Sheikh/
Primary Examiner, Art Unit 1615

hns

October 4, 2010